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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,790	01/27/2004	Chris Beard	1657/2035	2976

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TDAKA PRODUCTS
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EXAMINER	
BAUSCH, SARAE L	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,790	BEARD ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *5-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 01/17/2007.

Election/Restrictions

2. Applicant's election of group I (claims 1-4) in the reply filed on 01/17/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 5-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 01/17/2007.

Specification

4. The disclosure is objected to because of the following informalities: on page 56, line 19, "5-aza-2'-deoxyctyidine" is misspelled. The correct spelling is 5'aza-2'-deoxycytidine.

Appropriate correction is required.

5. The use of the trademarks GENEBANK (pg 17, table 1 and pg 26, table 2), UNIGENE (pg 17, table 1 and pg 26, table 2), GENECHIP (pg 17, line 17 and pg. 49, line 6), RNEASY (see pg 49, line 5), GENESPRING (pg. 49, line 12), AMPLITAQ (pg. 51, line 22), QIAQUICK (pg. 51, line 27) been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112- Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a). Claim 1 is vague and indefinite. Claim 1 is drawn to a method of identifying one or more nucleic acid sequences useful as a biomarker for a disease to be detected, however the final process step is identifying nucleic acid sequences exhibiting a significant increase in the expression level after demethylation treatment as compared to the expression level of the same nucleic acid sequence in the methylated state. Accordingly the claims are ambiguous because identifying nucleic acid sequences exhibiting a significant increase in the expression level after demethylation treatment as compared to the expression level of the same nucleic acid sequence in the methylated state will not *necessarily* result in identification of one more nucleic acid sequences useful as a biomarker for a disease to be detected. Therefore, the limitation in the preamble is not recited in the process steps, the metes and bounds of the claim are vague and indefinite, and it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

(b). Claim 1 and 2 are vague and indefinite for the recitation of "normal cells" in claim 1 and "normal sample" in claim 2. The term "normal" is a relative term which renders the claim indefinite. It is not clear what the "normal" features are, the type of cell or sample that is "normal" and what else "normal cells" or "normal sample" comprise. The term "normal cells" and "normal sample" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(c). Claim 2 recites the limitation "clinical sample" in line 2 and "the normal sample" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claim 2 depends from claim 1 and claim 1 does not recite a clinical or normal sample. Specifically, claim 2 recites the nucleic acid sequences from (c) in one or more clinical samples obtained from a subject having or suspected of having the disease to be detected significantly increases over the normal samples. However it is unclear what is significantly increased over the normal samples and what is actually be measured in the process steps. It is unclear if the methylation of the nucleic acids that were identified in step c in a clinical sample are significantly increased over the normal sample and at what point in the analysis is the methylation significantly increased. It is unclear if the methylation of nucleic acids after demethylation is signification increased in the clinical sample over the normal sample, if the methylation prior to demethylation in the clinical sample is significantly increased over the normal sample or if the overall methylation over time is increased in the clinical sample over the reference.

(d). Claims 2-4 depends from claim 1 and therefore are vague and indefinite for the reasons applied to claim 1.

Claim Rejections - 35 USC § 112-Scope of Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising the steps of (a) identifying one or more nucleic acid sequences useful as a biomarker by identifying a nucleic acid sequence that is down regulated in a disease cell compared to a control cell wherein the nucleic acid sequence comprises at least one methylated CpG site in a promoter-first exon region, (b) comparing the expression level of the nucleic acid sequence with expression level of the nucleic acid sequence that has been demethylated and (c) identifying those nucleic acid sequences exhibiting a significant increase in expression level after demethylation treatment wherein demethylation is accomplished using 5-aza-deoxycytidine, does not reasonably provide enablement for demethylation accomplished using a bisulfite compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claim is drawn to identifying one or more nucleic acid sequences useful as a biomarker by identifying a nucleic acid sequence that is down regulated in a disease cell compared to normal cell wherein the nucleic acid sequence comprises at least one methylated CpG site in a promoter-first exon region, comparing the expression level of the nucleic acid sequence with expression level of the nucleic acid sequence that has been demethylated and identifying those nucleic acid sequences exhibiting a significant increase in expression level after demethylation treatment. The claims are further limited to demethylation that is accomplished by bisulfite compound. The claims encompass methods of demethylation using a bisulfite compound.

Guidance in the Specification and Working Examples

The specification teaches that in association with the first step of identifying the CpG sites with great potential for diagnostic utility, a demethylation agent is used to treat cells or tissues. The specification teaches the demethylation agent is 5-aza-deoxycytidine (see page 35, lines 13-21). The specification teaches working examples of treatment of cells lines with demethylating agent, 5-aza-2'-deoxycytidine (see example 4, pg. 56). The specification teaches that bisulfite treatment, using a bisulfite compound, converts non methylated cytosine to uracil

leaving 5'methylcytosine unmodified (see page 30, lines 17-18). The specification does not teach a demethylation agent that is a bisulfite compound. The specification has no working example of using a bisulfite compound that demethylates the nucleic acid sequence.

The unpredictability of the art and the state of the prior art

Olek et al. (1996, as cited on IDS) teaches chemical modification of cytosine residues in the presence of sodium bisulfite, a bisulfite compound. Olek et al. teach that in the bisulfite reaction, cytosines are sulfonated and deaminated converting them to uracil sulphonate followed by basic pH, which completes the conversion from cytosines to uracil. Olek et al. teach that C5-methyl-cytosine are not modified under the conditions used. Olek et al. teach that after bisulfite treatment the chromosomal region of interest is PCR-amplified and the PCR products are sequenced and only methyl-cytosines are detected as cytosines whereas all unmethylated cytosines appear as thymidines (see page 5064, 1st column, 1st paragraph). Olek et al. therefore teaches that bisulfite compounds are not demethylating agents but are deaminating agents.

Vertino et al. (US Patent 6911306) teaches that a demethylating agent is an agent that directly or indirectly causes a reduction in the level of methylation of a nucleic acid molecule. Vertino et al. teach that demethylating agents include inhibitors of methylating enzymes, such as methylases and methyltransferases. Vertino et al. teach examples of demethylating agents, including 5-azadeoxycytidine, procanamide, and s-adenosyl homocysteine(see column 41, lines 43-64). Vertino et al. does not teach a bisulfite compound that is demethylating agent but does teach that sodium bisulfite deaminates cytosines that are not methylated (see column 37, lines 59-63).

Therefore, the prior art teaches that bisulfite compounds deaminate unmethylated cytosines but do not demethylate methylated cytosines. The prior art does teach demethylation by using demethylating agents such as 5- azadeoxycytidine.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to ability of a bisulfite compound to demethylate DNA and the knowledge in the prior art that bisulfite compounds deaminate cytosines but do not demethylate methylated cytosines, the quantity of experimentation in this area is extremely large. Although demethylating agents are readily available, as taught in the prior art and the specification, a demethylating agent that is a bisulfite compound is not known in the art. The skilled artisan would have to perform experiments to determine if any bisulfite compound could function as a demethylating agent. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the scope of the claims in an art whose nature is identified as unpredictable, the unpredictability of the art with regard to the mechanism and existence of a demethylating agent that is a bisulfite compound, the large quantity of research required, the absence of working examples, and the negative teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make and use a bisulfite compound that accomplishes demethylation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Daskalakis et al. (Blood, Oct 2002, Vol. 100, pp. 2957-2964).

With regard to claim 1, Daskalakis et al. teach low expression of p15 in biopsies from 10 myelodypastic syndrome (MDS) patients compared to 5 healthy individuals (see pg.2961, 2nd column, last paragraph). Daskalakis et al. teach the under-expression of p15 is associated with hypermethylation in the 5' region between positions –47 to +215 (see table 1 and pg. 2958, 2nd column, 1st paragraph) (identifying one or more nucleic acid sequences that are down regulated in disease cells compared to normal cells wherein the nucleic acid sequences comprise at least one methylated CpG site in a promoter-first exon region). Daskalakis et al. teach comparison of expression level of p15 before and after treatment with decitabine (demethylation agent) (see figure 6) (comparing expression level of nucleic acid sequence with expression level of nucleic acid sequence that have been demethylated). Daskalakis et al. teach up regulation of p15 after demethylation during decitabine treatment (see figure 6) (identifying nucleic acid sequence exhibiting significant increase in expression level after demethylation treatment as compared to expression level of the same nucleic acid sequence in the methylated state).

With regard to claim 2, Daskalakis et al. teach the methylation of p15 in MDS patients is significantly increased over the healthy individuals (see figure 4, and pg. 2961, 1st column, 1st

paragraph). It is noted that claim 2 was interpreted to require that the methylation prior to demethylation of the nucleic acid sample in the clinical samples was significantly increased compared to normal samples (see section 7(c) above).

With regard to claim 3, Daskalakis et al. teach hypermethylation spans the 5' region of p15, which encompass –47 to +215 (region that is within the range of 1000 base pairs upstream of the first exon and about 1000 base pair downstream of first exon) (see pg. 2958, 2nd column, 1st two paragraph and figure 5). Therefore, Daskalakis et al. teach identification of one CpG site within a promoter-first exon region that is within 1000 base pairs upstream of the first exon and about 1000 base pairs downstream of the first exon.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Sarae Bausch, PhD.
Examiner
Art Unit 1634